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Review Article

Pathophysiology and potential treatment modalities in women with recurrent urinary tract infection

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Abstract

Urinary tract infection (UTI) of the urinary bladder is a common bacterial infection that predominantly affects women, with many experiencing recurrent episodes. Recurrent UTIs (rUTIs) are associated with significant physical, psychological, and social difficulties. Further, they are closely related to lower urinary tract dysfunction (LUTD). LUTD affects bladder function and structure, thereby contributing to urinary urgency, frequency, and incontinence, which, in turn, increases the risk of recurrent infections due to impaired urothelial defense mechanisms. The current study explored the pathophysiology of LUTD in women with rUTIs. Potential treatments for rUTIs include long-term prophylactic antibiotics, probiotics, D-mannose, vaccines, small molecule inhibitors, and stem cell therapy. Moreover, it evaluated the use of platelet-rich plasma (PRP) therapy as a treatment modality for LUTD. PRP has regenerative and anti-inflammatory properties. Hence, it can be a promising option for enhancing urothelial barrier integrity and reducing infection recurrence. Repeated intravesical PRP injections are effective in improving bladder symptoms and decreasing UTI recurrences by enhancing the proliferative ability of the urothelium in patients with rUTIs. Further, this review examined the potential predictors of successful PRP treatment outcomes such as cytokine and urothelial biomarker levels, which provided insights into patient selection and individualized treatment strategies. Identifying the predictive biomarkers of treatment responsiveness is essential for optimizing PRP therapy. Hence, to improve the clinical outcomes and quality of life of patients with rUTIs, future research should focus on refining the use of PRP, exploring combination therapies, and validating biomarkers.

Keywords: *Biomarkers, Lower urinary tract dysfunction, Platelet-rich plasma, Recurrent urinary tract infection, Women*

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Introduction

Urinary tract infection (UTI) of the urinary bladder is among the most common bacterial infections in humans, and it affects approximately 150 million people globally each year [1]. Women are more likely to experience UTIs, with 30%–50% having a UTI episode during their lifetime. Moreover, up to 50% of them will develop recurrent infection within the next 6 months [2]. Recurrent UTIs (rUTIs) are defined as at least two episodes of infection with pyuria or a positive bacterial culture within the last 6 months or three episodes within the last 12 months. People with rUTIs present with a severe health condition that causes continuous physical, mental, and social difficulties [3].

Lower urinary tract dysfunction (LUTD) includes various conditions affecting the structure and function of the bladder and urethra, which causes symptoms such as urinary urgency and frequency, nocturia, and incontinence [4]. Based on a previous study, 90% of women with rUTIs had LUTDs including bladder neck dysfunction, detrusor dysfunction, and pelvic floor muscle issues [5]. Further, LUTD was found to be associated with a risk of rUTIs due to impaired bacterial washout and weakened innate defense mechanisms. These infections not only exacerbate LUTD but also contribute to chronic inflammation and tissue damage, further impairing bladder function and reducing the quality of life [6].

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Platelet-rich plasma (PRP) therapy is usually applied in medical and surgical fields because of its potent regenerative and anti-inflammatory effects on damaged or inflammatory tissues [7]. PRP contains several growth factors that stimulate cell proliferation, differentiation, and angiogenesis, all of which are essential for tissue regeneration and healing [7,8]. rUTIs are often associated with changes in the urothelial barrier and regenerative deficits in women. Previous studies have shown that repeated intravesical injections of PRP not only enhance the structural integrity of the urothelium but also reduce the frequency of infections [9-12].

The current review aimed to explore underlying LUTDs and their potential treatment modalities in women with rUTIs. Further, this study evaluated the efficacy of PRP injection in treating rUTIs and the potential predictive factors of treatment outcomes.

Investigating the underlying lower urinary tract dysfunctions in women with recurrent urinary tract infections

Urine culture results: Bacterial culture and white blood cell count

UTIs are among the most common infections in humans, and they primarily affect the urethra, bladder, and kidneys. The clinical symptoms of UTI in the urinary bladder include frequent urination, micturition difficulties, and burning sensation during urination [13]. The diagnostic methods for UTIs include routine urinary tests for nitrites and leukocyte esterase and urine culture. Among these modalities, urine culture can provide the most direct evidence for UTI diagnosis [14]. Bacterial culture can identify specific pathogens, which is essential for administering targeted antibiotic therapy. Uropathogenic *Escherichia coli* (UPEC) is the leading cause of UTIs. UPECs can develop intracellular bacterial communities (IBCs) in the superficial umbrella cells of the bladder urothelium. IBCs are biofilm-like structures that have protective effects against antibiotics and immune defenses. The persistence of IBCs can lead to chronic infection and is believed to be an important factor of rUTIs [15,16].

Elevated white blood cell (WBC) counts in the urine (referred to as pyuria) can indicate UTI or bladder inflammation. A hemocytometer reading of ≥10 WBC/mm^3 suggests significant pyuria. Meanwhile, based on manual microscopy, a value of ≥8 WBC per high-power field can reliably predict a positive urine culture. In automated microscopy, a value of >2 WBC per high-power field indicates significant pyuria, which suggests inflammation of the urinary tract [14].

Urinary biomarkers: Inflammatory cytokines

rUTIs pose significant diagnostic and management challenges. A recent research emphasizes the potential of urine biomarkers to enhance the detection and prediction of rUTIs. Urinary prostaglandin E2 is a potential biomarker of rUTI in postmenopausal women [17]. A consensus model incorporating neutrophil gelatinase-associated lipocalin, interleukin (IL)-8, and IL-1β had a strong diagnostic accuracy for UTIs, with a sensitivity of 84% and specificity of 91%. Hence, these biomarkers can be used in identifying rUTI [18]. IL-6 and IL-8 are the most extensively studied biomarkers and are frequently elevated in the urine during acute UTIs. In addition, biomarkers such as chemokine ligand 1 (CXCL-1), soluble tumor necrosis factor receptors 1 and 2, and myeloperoxidase-to-creatinine ratio can also be utilized for diagnosing UTIs. However, their clinical application must be further evaluated [19]. Recent studies have investigated the potential of urinary biomarkers in the diagnosis and management of LUTD and UTIs. The urine biomarkers CXCL-1 and IL-8 can help distinguish detrusor overactivity from UTIs in women with overactive bladder symptoms. In addition, urinary total antioxidant capacity and prostaglandin E2 levels are positively correlated with voiding detrusor pressure in patients with detrusor underactivity [20]. Measuring urinary cytokine levels can be a noninvasive diagnostic tool for monitoring the severity of LUTD and treatment response in women with rUTIs. The identification of these biomarkers can facilitate more precise treatments and decrease the need for antibiotics [21]. Nevertheless, large-scale clinical trials must be performed to validate the use of these biomarkers in guiding management strategies.

Videourodynamic study results

Videourodynamic study (VUDS) combines fluoroscopic imaging and traditional urodynamic testing to evaluate bladder function and the structural integrity of the lower urinary tract in real time. In women with LUTD and rUTIs, VUDS can provide critical insights into bladder storage and voiding function and identify any underlying anatomical or functional abnormalities [22]. VUDS has a high identification rate for LUTD in women with rUTIs. Up to 90% of these patients experience different types of LUTD such as detrusor underactivity, dysfunctional voiding, overactive bladder, and inadequate pelvic floor muscle relaxation [5,23]. Moreover, VUDS can detect bladder outlet obstruction or urethral dysfunction, which may be caused by chronic inflammation, scar tissue formation, or pelvic floor dysfunction due to repeated infections [24]. It is essential to identify these abnormalities because they can significantly influence treatment decisions. In particular, VUDS is helpful in patients with symptoms that cannot be relieved with the initial treatment or those who may require invasive procedures [25]. Overall, VUDS can provide crucial information on the precise diagnosis and management of LUTD and UTIs.

Bladder biopsy: Urothelial barrier, inflammatory, apoptotic, and proliferative markers

Bladder biopsy is a valuable tool for assessing the structural and cellular changes in the bladder that can be the underlying mechanism associated with LUTD in women with rUTIs. Chronic infections can damage the urothelial barrier, which is the protective lining of the bladder that prevents bacteria and toxins from penetrating the underlying tissue layers. Women with rUTIs often present with loss of urothelial integrity, which is believed to play a key role in the development of LUTD [16,26]. The urothelium has a high regenerative capacity in response to bacterial or chemical injury [27]. Moreover, it is rich in specific proteins that are crucial for maintaining the barrier function. Uroplakins (UPIa, UPIb, UPII, and UPIII) are transmembrane proteins that form

hexagonal plaques on the apical surface of umbrella cells, thereby creating a permeability barrier and providing structural stability. Zonula occludens-1 (ZO-1) is a tight junction protein that maintains cell–cell adhesion and prevents paracellular permeability. E-cadherin is essential for cell adhesion and maintenance of the urothelial barrier [28]. Women with rUTIs exhibit significant deficits in the expression of key urothelial proteins, including uroplakins, ZO-1, E-cadherin, and various cytokines [11,29]. These changes weaken the integrity and function of the urothelial barrier, making it more susceptible to bacterial invasion and recurrent infections.

rUTIs are associated with chronic inflammation and increased apoptosis of urothelial cells, as evidenced by elevated inflammatory protein and apoptotic marker levels in the bladder tissues [30]. In addition, the expression of the cell proliferation proteins CD34, SHH, and TP63 in the urothelium of patients with rUTIs significantly decreased. Meanwhile, the expression of apoptotic proteins BAD, BAX, and caspase-3 significantly increased [29]. Moreover, inflammatory signals such as p38 mitogen-activated protein kinase and tumor necrosis factor alpha (TNF-α) are associated with the promotion of urothelial cell apoptosis [31]. By analyzing these markers in bladder biopsy specimens, researchers can better understand the cellular and molecular changes causing LUTD in women with rUTIs. This information is critical for developing targeted therapies that aim to restore urothelial integrity and reducing inflammation.

Host defense mechanism and recurrent urinary tract infections in women

Host defense in the urinary tract

The innate immune system is the first line of defense against pathogens in the urinary tract. Neutrophils and macrophages are important in promoting the initial response in UTIs. Neutrophils are immediately recruited to the site of infection by proinflammatory cytokines such as CXCL1, IL-6, and TNF-α. Further, they form the neutrophil extracellular traps, which can trap and kill bacteria [32]. Macrophages have various functions. For example, they promote pathogen clearance and cytokine production and interact with other immune cells. Macrophages can polarize into the M1-like (proinflammatory) phenotype or the M2-like (anti-inflammatory) phenotype in response to the pathogen-associated molecular patterns and damage-associated molecular patterns present during UTIs [33]. Patients with immunodeficiency were more likely to experience frequent and severe rUTIs [34]. Toll-like receptors recognize pathogens and induce a robust inflammatory immune response. Patients with specific toll-like receptor polymorphisms may have a reduced ability to recognize pathogens in the bladder, leading to a higher prevalence of rUTIs [35].

T cells, particularly T helper (TH) cells, mediate the adaptive immune response during UTIs. Enhancing the TH type 1 cell response could better control the bacterial burden in the bladder [36]. TH type 2 cells promote epithelial repair via the expansion of IL-4-secreting T cells. However, this response can also inhibit bacterial clearance by suppressing interferon gamma production [37]. In addition, tissue-resident memory T cells accumulate in the bladder after the primary UPEC infection, which provides long-term immunity against recurrent infections [38].

Role of estrogen in host defense and recurrent urinary tract infection

Estrogen plays a complex role in host defense, affecting both innate and adaptive immune responses. These include (1) modulating macrophage differentiation, recruitment, and polarization and cytokine secretion; (2) enhancing neutrophil inflammatory responses; (3) influencing dendritic cell differentiation and function; (4) regulating natural killer cell activity; and (5) affecting both T- and B-cell development and function [39]. Reduced estrogen levels can result in decreased recruitment and immune cell function. rUTIs in postmenopausal women are influenced by the decline in estrogen levels, which affect the host defense mechanisms. Estrogen enhances antimicrobial peptides (AMPs) and epithelial integrity in the urothelium. Estrogen supplementation may reduce the risk of rUTIs in women [40].

Estrogen therapy, particularly topical estrogen, has become an important intervention for preventing rUTIs in postmenopausal women. A previous research has shown that topical estrogen can reduce the frequency of UTIs from 5 to 0.5–2 infections per year [41]. Topical estrogen, particularly at doses ≥850 μg/week, is more effective in preventing rUTIs than oral estrogen [42]. In addition, vaginal estrogen therapy reduces the risks associated with long-term antibiotic use. Hence, it is considered the first-line nonantibiotic treatment [43]. Estrogen can also influence the urogenital microbiome, thereby promoting the production of beneficial *Lactobacillus* that is associated with a reduced susceptibility to rUTIs [44]. Overall, estrogen therapy can be a promising approach to managing rUTIs in women.

Aging, diseases, and recurrent urinary tract infection

Age-related alterations in the urinary tract, such as bladder atrophy and changes in urothelial cells, facilitate bacterial colonization and persistence. Aging significantly affects the prevalence and characteristics of rUTIs in older adults, particularly women [45]. Postmenopausal women experience higher rates of rUTIs due to hormonal changes, comorbidities, and decreased physical health. Women aged 70–89 years are most affected by rUTIs. Comorbidities such as diabetes, hypertension, and sarcopenia are common in older women with rUTIs [46,47]. Older adults typically present with chronic diseases such as diabetes mellitus, kidney disease, and cognitive impairments, all of which can contribute to the increased incidence of UTIs. In patients with diabetes, hyperglycemia and glycosuria provide a favorable environment for microbial growth. Insulin signaling is involved in the production of AMPs in high-glucose environment, thereby complicating the association between hormonal balance and UTI susceptibility [48]. Cognitive impairments, including dementia, can also increase the risk of UTI due to urinary incontinence, urination difficulties, or increased postvoid residual volume. Patients with cognitive decline may have difficulty recognizing the symptoms of infection, leading to delayed diagnosis and treatment. Further, functional impairments can result in poor hygiene practices and increased

reliance on catheters, which are significant risk factors of UTIs [49,50].

Neurogenic factors significantly contribute to the development of rUTIs in patients with neurogenic LUTD. A neurogenic bladder refers to bladder dysfunction caused by neurological conditions such as spinal cord injuries, multiple sclerosis, Parkinson's disease, and other central nervous system disorders. This dysfunction can lead to urinary retention, incomplete bladder emptying, and urinary incontinence, all of which create favorable conditions for bacterial growth [51]. In addition, a neurogenic bladder impairs the urothelial barrier function. This leads to a reduced expression of barrier proteins and increased susceptibility to bacterial adherence and invasion, thereby contributing to rUTIs [11]. Patients with neurogenic bladder have a significantly higher incidence of rUTIs than the general population. The key risk factors include vesicoureteral reflux (VUR), bladder compliance, and catheterization practices. High-grade VUR increases the risk of UTIs. Moreover, low bladder compliance and late or infrequent clean intermittent catheterization contribute to higher rates of rUTIs [52,53].

Prevention of recurrent urinary tract infections

rUTIs pose a significant burden on healthcare systems and affect the quality of life. Effective prevention strategies are essential for reducing the frequency of these infections. The potential of various approaches for managing UTI recurrence has been explored.

Behavioral modification

The majority of acute cystitis cases in women are often associated with lifestyle factors such as inadequate hydration, prolonged urinary retention, and chronic constipation. Preventing rUTIs can be effectively achieved through various behavioral modifications, including increasing water intake, practicing postcoital micturition, maintaining proper menstrual hygiene, and addressing constipation [54]. These behavioral modifications are both practical and adaptable for women to incorporate into their daily routines to effectively reduce the risk of rUTIs.

Long-term prophylactic antibiotics

Long-term prophylactic antibiotics are commonly used for preventing rUTIs, particularly in individuals with a history of frequent infections. Previous studies have revealed that low-dose antibiotics can significantly reduce the incidence of UTIs in at-risk populations [55]. However, this strategy raises concerns regarding antibiotic resistance and its impact on the microbiome. Thus, cautious evaluation and monitoring are essential when using long-term antibiotic therapy.

Probiotics

Probiotics are emerging as a promising nonantibiotic method for preventing rUTIs. Several studies have revealed that probiotics may help restore the natural urogenital microbiota. *Lactobacillus* strains inhibit the growth of uropathogen and enhance the immune response, potentially reducing UTI recurrence [56]. A double-blind, placebo-controlled study revealed that both vaginal probiotics and the combination of oral and vaginal probiotics effectively reduced the incidence of symptomatic UTI episodes [57]. Nevertheless, the efficacy of probiotic varies per strain, and its potential side effects require cautious monitoring. Nevertheless, further research should be performed to optimize the clinical use of probiotics in UTI management [58].

D-mannose

D-mannose is a type of sugar found in certain fruits and vegetables. It prevents UTIs by competitively inhibiting bacterial adherence to urothelial cells and promoting the flushing of pathogens from the urinary tract, thereby reducing the risk of infections [59]. Previous studies have found that compared with antibiotics or the absence of treatment, D-mannose can reduce UTI recurrence rates, prolong UTI-free periods, and improve quality of life [60,61]. However, daily D-mannose did not decrease the incidence of rUTIs in women who developed another clinically suspected infection in primary care settings in a randomized clinical trial. Therefore, the use of D-mannose as a prophylaxis is not recommended for this patient group [62].

Vaccine

Previous clinical trials have shown that several vaccines are safe and have immunogenicity. The European Association of Urology guidelines recommend the oral vaccine OM-89, a lyophilized preparation of *E. coli* membrane proteins, as it is a safe and effective prophylactic option for rUTIs [63,64]. ExPEC4V, a bioconjugate vaccine containing the O-antigens of four *E. coli* serotypes, elicited robust antibody responses in a phase 1b trial [65]. A phase 1 study revealed that an adjuvant *E. coli* adhesin vaccine had good safety and immunogenicity in women with rUTIs [66]. These advancements indicate that vaccines may play an increasing role in preventing rUTIs and reducing antibiotic use.

Small-molecule inhibitors

Recent research has focused on the development of small-molecule inhibitors specifically targeting UPEC for UTI treatment. Curli are bacterial surface-associated amyloid fibers that enhance UPEC colonization and facilitate UPEC biofilm formation. The small-molecule inhibitor FN075 inhibits curli biogenesis, disrupts biofilm formation, and reduces virulence in a mouse urinary tract infection model [67]. ECIN is a small-molecule inhibitor that can enhance copper toxicity against UPEC and effectively disrupt UPEC biofilm formation [68]. FimH is a key protein involved in UPEC entry into the bladder. Researchers have conducted a high-throughput screening of natural products to identify potentially effective FimH inhibitors. In parallel, a computational model was used to design and screen small molecules that target FimH [69,70]. Despite this progress, the use of small-molecule inhibitors is currently in the early experimental stage, and their long-term efficacy should be fully established.

Stem cell therapy

Stem cells can differentiate into various cell types, including bladder smooth muscle and epithelial cells, which facilitate the repair of damaged tissues [71]. Mesenchymal stem cells (MSCs) exhibit anti-inflammatory properties that can help alleviate the symptoms of interstitial cystitis/

bladder pain syndrome (IC/BPS) [72]. The autologous stromal vascular fraction, which is rich in stem cells, can improve quality of life and reduce symptoms in patients with IC [73]. A phase I clinical trial showed that MSCs derived from human embryonic stem cells are safe. These cells were injected transurethrally into patients with IC, leading to temporary pain improvement, and adverse effects were not reported [74]. Stem cells have been widely utilized in various fields of tissue engineering and regenerative medicine because of their regenerative capacity and anti-inflammatory properties. These mechanisms may also be applicable in UTI treatment.

Intravesical platelet-rich plasma injection for recurrent urinary tract infections

The regenerative properties of PRP have been beneficial for various urological disorders. By promoting tissue repair and enhancing local immune responses, intravesical PRP injection is emerging as a novel and promising treatment strategy for rUTIs. The following sections will explore the efficacy of intravesical PRP injections from different perspectives, thereby highlighting their potential in clinical practice.

Decrease in the incidence of urinary tract infection after platelet-rich plasma injection

A randomized clinical trial showed that intravesical PRP injection significantly reduced the recurrence of bacterial cystitis in women, with only one recurrence in the PRP group and four in the control group after 12 months [75]. In addition, after four PRP injections, the frequency of rUTI episodes per month significantly decreased compared with that at baseline [12].

Improvement of bladder symptoms and voiding parameters after platelet-rich plasma injection

PRP injections resulted in improved symptoms in patients with IC/BPS. The mean IC symptom index, IC problem index, global response assessment (GRA) score, and visual analog scale score of patients with IC/BPS significantly improved after four repeated PRP treatments [33]. In addition, patients with IC/BPS or those with rUTI had a significantly higher functional bladder capacity at 3 months after the 4th PRP injection [76-78]. In patients with rUTI, a successful PRP treatment was defined as ≤2 episodes of UTI recurrence during 1 year of follow-up. The treatment success group had a significantly higher voided volume, lower postvoid residual volume, and greater voiding efficiency than the treatment failure group [12].

Changes in urine biomarker levels after platelet-rich plasma injection

In patients with IC/BPS, the urinary levels of nerve growth factor, matrix metalloproteinase-13, and vascular endothelial growth factor (VEGF) significantly decreased. Meanwhile, the platelet-derived growth factor (PDGF)-AB levels significantly increased after the 4th PRP treatment. The urinary VEGF levels of all patients with IC/BPS decreased after the first PRP injection and remained low by the fourth PRP treatment [78]. At baseline, patients with rUTI had a significantly lower urinary levels of growth factors, including nerve growth factor and VEGF, than healthy controls. However, they had significantly higher brain-derived neurotrophic factor levels. The urinary BDNF level after treatment decreased compared with that at baseline [10].

Effect of cytokine concentrations in platelet-rich plasma on the treatment outcome of recurrent urinary tract infection

The cytokine levels in PRP are essential for achieving successful treatment outcomes. Patients with rUTI who had successful outcomes had significantly lower TNF-α levels in the PRP and remarkably lower EGF, PDGF-AA, and TGF-β2 levels. In addition, the PDGF-AA, PDGF-AB/BB, and TGF-β1 levels were significantly positively correlated with GRA. Meanwhile, the TNF-α level was negatively correlated with GRA. The number of UTI episodes within 1 year after PRP treatment was negatively correlated with TGF-β2 levels [76].

Ultrastructural changes in the bladder urothelium in recurrent urinary tract infection and after platelet-rich plasma injection

Patients with rUTI exhibited defects in the umbrella cell integrity, widened tight junctions, IBCs, and elevated levels of inflammatory cytokines such as IL-6 and IL-8. These defects result in increased permeability and greater vulnerability to infections [10,79]. PRP injections can enhance bladder recovery, with 25%–42% of patients presented with improvements in bladder defects [10]. Intravesical PRP injections can promote urothelial cell proliferation and enhance the expression of barrier function proteins, including Ki-67 [Figure 1] and E-cadherin [Figure 2]. After PRP treatment, 63.6% of patients with rUTI experienced a reduction in infection episodes and significant improvements in urothelial markers including CD34, CK20, M2, and M3 [9,77]. In contrast, although PRP is promising, not all patients have a similar response, and some may still exhibit persistent urothelial defects after treatment [80]. Hence, intravesical PRP injections can effectively enhance urothelial health and reduce UTI recurrence in patients with persistent rUTIs.

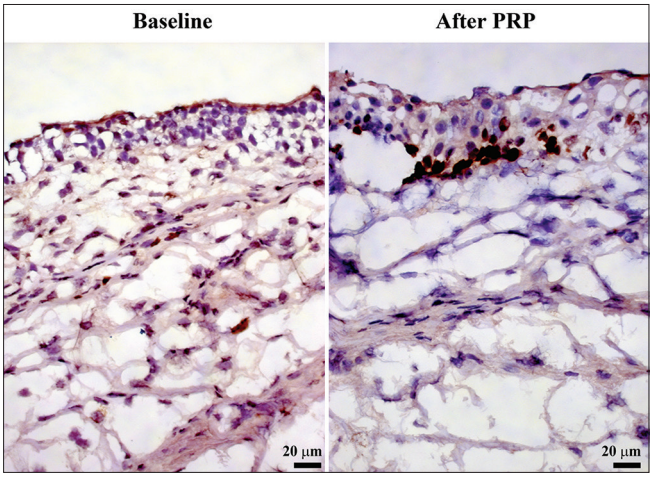

Figure 1: Platelet-rich plasma (PRP) treatments enhance Ki-67 expression in patients with recurrent urinary tract infections (rUTIs). Immunohistochemistry demonstrated elevated Ki-67 protein expression (brown staining) in the urothelial nuclei of patient with rUTIs after PRP treatments. The nuclei were counterstained with hematoxylin

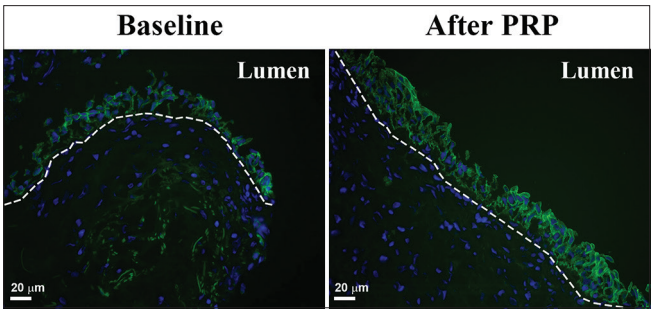

Figure 2: Induction of E-cadherin expression in patient with recurrent urinary tract infection (rUTI) after platelet-rich plasma (PRP) treatments. Immunofluorescence staining revealed an increase in E-cadherin protein expression (green fluorescence) in the urothelium following PRP treatments in patient with rUTIs. The nuclei were counterstained with DAPI: 4',6-diamidino-2-phenylindole. PRP: Platelet-rich plasma

However, further research should be performed to optimize the treatment protocols.

Investigating the predictive factors of patients who respond to platelet-rich plasma injections

Patients have different responses to PRP injections. Identifying the predictive factors of PRP responsiveness can help individualize treatments and optimize therapeutic outcomes. As it can be collected noninvasively, is rich in metabolites, and can reflect systemic biochemical imbalances, urine is an ideal sample for identifying biomarkers [81]. Mass spectrometry (MS) is a key technique for identifying novel biomarkers in urine samples for various diseases. It has a high sensitivity and specificity in analyzing proteins, peptides, and metabolites [82-86]. MS-based techniques can be used to identify potential biomarkers for PRP treatment and to determine which patients are suitable for PRP therapy. In addition, newly discovered biomarkers can be integrated into the ingenuity pathway analysis to gain a deeper understanding of their roles in biological processes and disease mechanisms. Ingenuity pathway analysis can also map these biomarkers onto established molecular pathways, networks, and interaction maps, thereby offering valuable insights into their functional significance.

RNA sequencing using next-generation technology is a powerful tool for biomarker discovery in cancer and other diseases [87]. Research on rUTIs has focused on urothelial innate immunity mechanisms, as disturbances in these systems may increase susceptibility to recurrence [21]. RNA sequencing analysis of urothelial cells can provide insights into the host immune response and identify potential biomarkers for predicting urothelial regeneration and response to PRP treatment.

Limitations of platelet-rich plasma injection for recurrent urinary tract infections

The current source of PRP for intravesical injection is autologous, with a reported treatment success rate of 51.5% [12]. Patients with rUTI are often older and may have compromised immune systems, which could potentially impact the therapeutic efficacy of PRP. In addition, ethical considerations present another challenge, as the absence of a placebo control arm in PRP studies for rUTIs makes it difficult to accurately evaluate its effectiveness compared to standard treatments.

Conclusion

This review examined the underlying LUTDs and their potential treatment modalities in women with rUTIs. Further, it evaluated the efficacy of PRP as a novel therapeutic approach. Chronic inflammation, changes in urothelial barrier function, and microbial resistance are the central components that contribute to infection recurrence. PRP therapy promotes tissue healing, enhances immune responses, and restores urothelial integrity. Hence, to develop targeted and effective therapies, it is important to understand the pathophysiological mechanisms of LUTD in women with rUTI. Nevertheless, future research should focus on optimizing PRP protocols, exploring combination therapies, and identifying biomarkers that can predict patient response. Such advancements can significantly improve the clinical outcomes and quality of life in women with rUTIs.

Data availability statement

No datasets were generated or analyzed in the course of this study.

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Conflicts of interest

Dr. Hann-Chorng Kuo and Dr. Yuan-Hong Jiang, the editorial board members at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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